

## REMARKS

### *Claim Amendments*

Claims 90 and 96 have been amended. Claims 98-104 have been added. Claims 46-48 and 97 have been canceled without prejudice or disclaimer to the subject matter therein. Upon entry of the foregoing amendment, claims 43-45, 88-96 and 98-104 will be pending in the application.

Support for amended claim 90 and new claim 99 may be found, for example, on page 39, lines 1-4 and 15-17 and Figure 1.<sup>1</sup> Claim 96 is amended to reflect cancellation of claim 46. Support for new claims 98 and 104 may be found, for example, on page 39, lines 18-19. Support for new claims 100-101 may be found, for example, on page 39, lines 18-19 and 24-26. Support for new claims 102-103 may be found, for example, on page 39, lines 27-28.

Applicants respectfully request entry of the foregoing above amendment and submit that the above amendment does not constitute new matter.

### *Withdrawn Rejections*

Applicants appreciate the withdrawal of the previous rejections under 35 U.S.C. §§ 102(b) and 103(a).

### *Rejections Under 35 U.S.C. § 103(a)*

Claims 43-45 and 88-89 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Merril et al. (U.S. Patent No. 5,811,093, hereinafter “Merril”), in view of Byrd et al. (Applied Poultry Science, hereinafter “Byrd”), Berchieri et al. (Res. Microbiol., hereinafter “Berchieri”), Taylor et al. (U.S. Patent No. 2,851,006, hereinafter “Taylor”), and Holzman (Genetic Engineering News, hereinafter “Holzman”).

Applicants respectfully traverse this rejection.

The Office Action asserts that Merril discloses a method for topically treating animals (e.g., livestock) with a composition comprising at least one bacteriophage. Office Action, page 4. The Office Action maintains that “livestock” includes “freshly-hatched birds.” *Id.* The Office Action acknowledges, however, that Merril does not disclose “applying the bacteriophage specifically to a freshly-hatched bird.” *Id.* To supply these missing teachings, the Office Action relies on Byrd, Berchieri, Taylor and Holzman.

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<sup>1</sup> The citations referred to herein are taken from the substitute specification filed on May 28, 2004.

As an initial matter, Applicants point out that Merril relates to a general method of bacteriophage *therapy* in animals comprising administering a genetically engineered bacteriophage capable of delaying inactivation by an animal's host defense system.<sup>2</sup> Therapy relates to the treatment of an infection. *See* Declaration Under 37 C.F.R. § 1.132 of Dr. Gary Pasternack ("Declaration of Dr. Pasternack"), ¶ 9; *see also* Declaration of Dr. Pasternack, ¶ 11 ("The Merril reference relates to therapy for animals having bacterial infections.") Merril is limited to a method of treating animals (in general) by administering a bacteriophage specific for particular pathogenic bacteria, the bacteriophage having been modified for the purpose of prolonging phage viability in the body.<sup>3</sup> Merril also teaches that his bacteriophage "are administered until successful elimination of the pathogenic bacteria is achieved." Col. 11, lines 1-3. Accordingly, Merril teaches using his modified bacteriophages to evade the host immune system in animals infected with pathogenic bacteria to improve therapy. Declaration of Dr. Pasternack, ¶ 12.

The claimed invention is directed to applying bacteriophage to "freshly-hatched" birds. At the time of hatch, a bird's digestive tract is essentially sterile. *See* Declaration of Dr. Pasternack, ¶ 8; *see also* Byrd, page 76, first column, first full paragraph. "Freshly-hatched" birds are therefore not infected by pathogenic bacteria and therefore do not require "therapy." *See* Declaration of Dr.

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<sup>2</sup> *See e.g.*, Abstract ("The present invention is directed to bacteriophage *therapy*..."); col. 3, lines 64-67 ("The phage *therapy* of this invention will therefore be useful either as an adjunct to standard anti-infective therapies, or as a stand-alone therapy."); col. 8, lines 4-5 ("The second embodiment of the present invention is the development of methods to *treat bacterial infections*..."); col. 8, lines 14-18 ("While it is contemplated that the present invention can be used to *treat any bacterial infection* in an animal, it is particularly contemplated that the methods described herein will be *very useful as a therapy* (adjunctive or stand-alone) in infections caused by drug-resistant bacteria."); col. 9, lines 39-41 ("Thus, all *bacterial infections* caused by bacteria for which there is a corresponding phage can be treated using the present invention."); col. 9, lines 54-56 ("The anti-HDS modified bacteriophage of the present invention can be used as a *stand-alone therapy* or as an *adjunctive therapy* for the *treatment of bacterial infections*."))

<sup>3</sup> *See, e.g.*, Col. 1, lines 22-26 (The "anti-HDS" bacteriophages of Merril "have a longer survival time in an animal's body than the corresponding wild-type bacteriophage, and that in turn allows the modified phage to be more effective than the wild-type phage at treating (or assisting in the treatment of) a bacterial infection."); col. 3, lines 56-60 ("This allows the novel phages to survive for longer periods of time in the circulation and the tissues than the wild-type phage, thereby prolonging viability and making these modified phages more efficient at reaching and invading the bacteria at the site of an infection."); col. 5, lines 4-7 ("Thus, the object of the present invention is to develop bacteriophages that are able to delay inactivation by the HDS. This will prolong phage viability in the body.").

Pasternack, ¶ 12. Because Merril is directed only to “therapy” of infected animals and does not teach or suggest applying bacteriophage to “freshly-hatched” birds (i.e., uninfected birds), one would have no reason to use the method of Merril to achieve the claimed methods. *See id.* Accordingly, Merril teaches away from the claimed invention.

Byrd does not remedy the deficiencies of Merril. The Office Action cites Byrd for the proposition that broiler breeder flocks and hatcheries are reservoirs of salmonellae and potential sources of *Salmonella* infection for day-old chicks. Office Action, page 4. Byrd, however, does not teach or discuss any method for addressing this issue, let alone mention the use of bacteriophages. Byrd teaches that a newly-hatched bird’s digestive tract is essentially sterile. *See* Byrd, page 76, first column, first full paragraph. Byrd also teaches that “[d]ay-of-hatch chicks that had not been inoculated [with *Salmonella*] and had no contact with birds given *Salmonella* … were negative for *Salmonella* after 17 days.” Byrd, page 76, under “Experimental Procedures.” Byrd does not indicate that day-old chicks are infected, nor does Byrd teach that day-old chicks are candidates for treatment. *See* Declaration of Dr. Pasternack, ¶ 13. Accordingly, the combination of Byrd with Merril provides no reason to apply the bacteriophage therapy of Merril to uninfected chickens.

Berchieri also fails to remedy the deficiencies of Merril and Byrd. Indeed, Berchieri, like Merril, relates to treatment of infection.<sup>4</sup> In particular, Berchieri inoculates chickens with *Salmonella* to establish a *Salmonella* infection and then applies bacteriophage to treat the *Salmonella* infection. *See* Declaration of Dr. Pasternack, ¶ 14. This is contrary to the claimed invention which relates to applying bacteriophages to “freshly-hatched” birds (i.e., uninfected birds). *Id.* Accordingly, the combination of Berchieri with Merril and Byrd still provides no reason to apply the bacteriophage therapy of Merril to uninfected chicks.

Taylor does not remedy the deficiencies of Merril, Byrd and Berchieri. Indeed, Taylor does not teach or suggest the step of “applying at least one bacteriophage to at least one freshly-hatched bird before transferring said at least one freshly-hatched bird to a chicken house.” *See* Declaration of Dr. Pasternack, ¶ 16. Rather, Taylor is directed to methods of introducing bacteriophage *into*

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<sup>4</sup> Applicants agree with the Office Action’s assertions that Berchieri teaches infection of chicks. Indeed, it is Berchieri himself who infects chicks with *Salmonella* as part of his experimental protocol.

eggs, not applying bacteriophage to hatched birds.<sup>5</sup> Accordingly, the combination of Taylor with Merril, Byrd and Berchieri still provides no reason to apply the bacteriophage therapy of Merril to uninfected chicks.

Holzman also fails to remedy the deficiencies of Merril, Byrd, Berchieri and Taylor. The Office Action states that Holzman “discloses using phages to target pathogens … as a way of potentially clearing the poultry yards of *S. enteriditidis*.” Office Action, page 5. Assuming Holzman discloses a method of using bacteriophages, Applicants submit that Holzman fails to disclose any specific method and/or steps for carrying out such a method of using bacteriophages. *See* Declaration of Dr. Pasternack, ¶ 17. To be sure, Holzman does not teach or suggest a method of applying bacteriophage to a bird at a particular stage of life — after hatching and before transferring the bird to a chicken house — as required by the claimed invention. *Id.* At best, Holzman is a generic reference that suggests applying bacteriophage for a variety reasons including at least therapy. *Id.* This disclosure alone, or in combination with the cited references, is insufficient to render the claimed invention unpatentable because the claims are limited to a specific application of bacteriophage neither taught nor suggested by Merril, Byrd, Berchieri, Taylor or Holzman.

Accordingly, Applicants submit that the references alone, or in combination, do not teach each and every claim element.

Applicants further submit that the Office Action fails to establish a *prima facie* case with respect to claims 88 and 89. Claim 88 is directed to the method of claim 43, and further comprises the step of applying at least one bacteriophage to the surface of an egg prior to hatching of the bird. Claim 89 is directed to the method of claim 43, and further comprises the step of transferring said bird to a chicken house after applying the bacteriophage. The Office Action includes claims 88 and 89 in the rejection, but fails to point out where these references teach or suggest the elements of claims 88 and 89. Applicants respectfully request clarification as to where the Examiner contends these elements are disclosed in the cited references.

In view of the foregoing, Applicants respectfully request withdrawal of the 103(a) rejection over Merril, Byrd, Berchieri, Taylor and Holzman.

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<sup>5</sup> Indeed, Taylor’s method “provides a method for increasing the percentage hatch of fowl eggs” by “introduc[ing] a small quantity of a selected bacteriophage, which is known to destroy the particular objectionable bacteria … **through the shell of the whole egg** and then incubate the treated egg.” Taylor, col. 1, lines 15-16 and 52-56. (emphasis added); *see also* Declaration of Dr. Pasternack, ¶ 16.

Claims 46-48 and 94-97 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Merril, as applied to claims 43-45 and 88-89 above, and further in view of Day et al. (U.S. Patent No. 4,851,240, hereinafter “Day”), Taylor, Byrd and Berchieri.<sup>6</sup>

Applicants respectfully traverse this rejection.

As discussed above, the methods of Merril in combination with Byrd, Berchieri and Taylor do not teach or suggest a method of “applying the at least one bacteriophage to at least one freshly-hatched bird before transferring said at least one freshly-hatched bird to a chicken house.” Furthermore, these references do not teach or suggest the method of claim 89.<sup>7</sup>

Day does not remedy the deficiencies of these references. Indeed, Day does not teach or suggest the step of “applying the at least one bacteriophage to at least one freshly-hatched bird” or the step of “transferring said bird to a chicken house after applying the bacteriophage.” Applicants also point out that Day relates to methods of controlling the microbial flora in ruminant livestock, and does not relate to methods of applying bacteriophages to chickens. *See, e.g.*, Office Action, page 2 (“Day et al., which discloses treating ruminant livestock with bacteriophage, does not teach treating poultry livestock with bacteriophage.”). Indeed, in every instance that Day specifically discusses administering drinking water (or food) containing bacteriophage, it is clear that Day is referring to ruminant livestock (e.g., cattle) and not poultry (e.g., chickens). *See* Applicants Response filed September 4, 2007, page 7.<sup>8</sup> While the combination of Merril and Day might lead one to consider using Merril’s genetically modified bacteriophage to treat ruminants with clostridial infections in their rumen, it would not lead one to orally administer the bacteriophage of Merril to freshly-hatched chickens which are not infected. Accordingly, contrary to the Office Action’s assertions, it would not have been obvious, in view of Day, to modify the methods of Merril to achieve the claimed invention.

In view of the foregoing, Applicants respectfully request withdrawal of the 103(a) rejection over Merril, Day, Taylor, Byrd and Berchieri.

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<sup>6</sup> Applicants note that claims 46-48 and 97 have been canceled herein.

<sup>7</sup> Claims 94 and 95 depend from claim 89.

<sup>8</sup> For example, Day discloses treatment of ruminant flora (column 4, lines 26-42), and specifically indicates infection of the rumen by *clostridia* followed by destruction of the infecting *clostridia* using bacteriophage (column 4, lines 38-40). *See* Declaration of Dr. Pasternack, ¶ 18.

Claims 90-93 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Taylor, in view of Cox et al. (J. Applied Poultry Res., hereinafter “Cox”) and Holzman.

The Office Action asserts that Taylor teaches a method of disinfecting infected eggs by submerging the eggs into a bacteriophage bath. Office Action, pages 9 and 10. The Office Action suggests that bacteria on the egg will be killed by the bacteriophage. *Id.* at page 10. The Office Action acknowledges, however, that Taylor does not teach spraying bacteriophage onto the surface of an egg. To supply this missing teaching, the Office Action relies on Cox and Holzman. The Office Action cites Cox for the proposition that “spray” sanitizing machines clean and disinfect eggs. *Id.* The Office Action asserts that Holzman teaches using phages to target pathogens that plague livestock, such as *Salmonella* in meat, poultry and eggs. The Office Action concludes that it would have been obvious to one of ordinary skill in the art to modify the methods of Taylor to disinfect contaminated/infected eggs by spraying phage instead of dipping the eggs into a phage bath. *Id.* The Office Action asserts that one would have been motivated to do so given the suggestion by Holzman to use phages to target pathogens that plague livestock and the teachings of Cox (spraying eggs with a disinfectant reduces the number of bacteria on eggs). *Id.*

Applicants respectfully disagree and traverse this rejection.

As an initial matter, Applicants point out that Taylor’s invention is directed to the introduction of bacteriophage into infected eggs to increase hatch percentage. Indeed, Taylor’s method “provides a method for increasing the percentage hatch of fowl eggs” by “introduc[ing] a small quantity of a selected bacteriophage, which is known to destroy the particular objectionable bacteria … *through the shell of the whole egg* and then incubate the treated egg.” Taylor, col. 1, lines 15-16 and 52-56.<sup>9</sup> (emphasis added). Accordingly, Taylor’s method of increasing hatch percentage depends on the introduction of bacteriophage into the egg. *See* Declaration of Dr. Pasternack, ¶ 20. Taylor’s method would therefore not lead one to perform a method of spraying bacteriophage onto the surface of eggs where the spray does not penetrate the egg shell. *Id.* To the extent that any bacteria on the surface of an egg may be incidentally killed by the method of Taylor, it would be completely irrelevant to the stated purpose of Taylor’s method.

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<sup>9</sup> *See also* Example 1 (directed to introducing bacteriophage into infected eggs to measure the percentage hatch favorably compared to uninfected control); Examples 2-3 (directed to introducing bacteriophage into infected eggs to measure the percentage hatch favorably compared to infected eggs).

Even assuming that bacteria on the surface of an egg is incidentally killed by the method of Taylor, which Taylor does not specifically teach, Taylor's method teaches away from the claimed methods. Taylor uses a syringe or pressure differential to introduce the bacteriophage into the egg. *See, e.g.*, col. 1, lines 58-63; *see also* Examples 1-3.<sup>10</sup> The eggs are then incubated for 22 days. *See* Examples 1-3. Taylor's method is therefore directed to treating eggs immediately (or shortly) after being laid. *See* Declaration of Dr. Pasternack, ¶ 21.

The claimed invention is directed to spraying bacteriophages at the hatchery, not where eggs are collected immediately (or shortly) after being laid, i.e., the egg collection site. *See* Declaration of Dr. Pasternack, ¶ 22.<sup>11</sup> Indeed, the invention relates to spraying bacteriophages before hatch so as to minimize bacterial contamination as the chicks hatch. *Id.* If one were to apply bacteriophages to the surface of an egg immediately (or shortly) after lay (i.e., not shortly before hatch), like Taylor, then the egg will be predisposed to recontamination prior to hatch and bacterial contamination will not be minimized at hatch. *Id.* Accordingly, even if Taylor's method incidentally kills bacteria on the surface of an egg, it would be not be useful in performing the claimed methods. *Id.*

Cox does not remedy the deficiencies of Taylor. Cox teaches that “a freshly laid egg is wet and warm, susceptible to rapid penetration by microorganism” and therefore recommends that “the appropriate chemical should be applied as soon as economically possible after lay.” Cox, page 234, first column; Cox, page 235, first column; *see also* Declaration of Dr. Pasternack, ¶ 23. While Cox might lead one to spray a sanitizer to an egg immediately (or shortly) after being laid, it would not lead one to spray a sanitizer at the hatchery so as to minimize bacterial contamination as the chicks hatch. *Id.* at ¶¶ 23-24. Accordingly, Cox suffers from the same limitations as Taylor.

Holzman does not remedy the deficiencies of Taylor and Cox. The Office Action states that Holzman “discloses using phages to target pathogens … as a way of potentially clearing the poultry yards of *S. enteriditidis*.” Office Action, page 10. Assuming Holzman discloses a method of using bacteriophages, Applicants submit that Holzman fails to disclose any specific method and/or steps for carrying out such a method of using bacteriophages. *See* Declaration of Dr. Pasternack, ¶ 17. To be sure, Holzman does not teach or suggest a method of spraying bacteriophage to eggs, wherein

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<sup>10</sup> When Taylor treats eggs by immersion in a liquid medium containing bacteriophage, the conditions ensure that bacteriophage are forced through the shell into the interior of the egg. *See, e.g.*, Taylor, col. 2, lines 3-21.

<sup>11</sup> *See also* Declaration of Dr. Pasternack, ¶ 7 (describing a typical poultry processing system).

said spraying occurs in a hatchery — as required by the claimed invention. *Id.* At best, Holzman is a generic reference that suggests applying bacteriophage for a variety reasons including at least therapy. *Id.* This disclosure alone, or in combination with the cited references, is insufficient to render the claimed invention unpatentable because the claims are limited to a specific application of bacteriophage neither taught nor suggested by Taylor, Cox or Holzman.

In view of the foregoing, Applicants respectfully request withdrawal of the 103(a) rejection over Taylor, Cox and Holzman.

**CONCLUSION**

In view of the foregoing, Applicants respectfully request an indication of allowance of all claims.

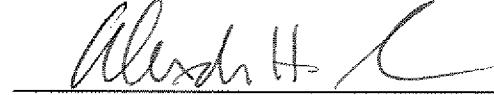
If the Examiner has any questions relating to this response, or the application in general, she is respectfully requested to contact the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

HUNTON & WILLIAMS LLP

Dated: May 13, 2008

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